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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,807	07/16/2001	Helen Rachel Crooke	GJE-65	2112

23557 7590 01/29/2003

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EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/830,807	CROOKE ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,18 and 19* is/are pending in the application.

4a) Of the above claim(s) *1-8,10-17 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group V in Paper No. 9 is acknowledged. The traversal is on the ground(s) that because there was unity in a PCT application, there should be unity in this application. Applicants claim that there is a single inventive concept.

This is not found persuasive because the claims presented in the instant application are not the same claims presented in the numerous previous PCT applications. Therefore, a different analysis must thereby occur. In this case, it is the examiner opinion that the instant claims do not form a single inventive concept since each group comprises separate and distinct functions that do not share substantial structural features disclosed as being essential to the utility of the invention. Therefore, applicants' argument the IPEA did not find lack of unity is not persuasive, since the IPEA examined different claims. Moreover, as stated in the previous action each product and method has different special technical features, therefore the restriction is maintained. Furthermore, as per application PCT GB 99/03721 the International Searching Authority found multiple groups of inventions, thus applicants' argument is not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 9 is drawn to operons obtainable from E.coli K1 or a homologue thereof wherein the homologue may be a functional fragment thereof. However, the written description in this case only sets forth specific sequences such as SEQ ID NO:12 and the written description is not commensurate in scope with the claims drawn to homologues thereof or functional fragments thereof.

Furthermore, it is unclear how to define homologues thereof or functional fragments thereof. Neither the claims nor the specification teach how to obtain a homologues thereof or functional fragments thereof by deletion, substitution or insertion of one or more amino acids. There is no guidance as to what amino acids may or may not be changed without causing a detrimental effect to the homologues thereof or functional fragments thereof as claimed. The claims broadly teach homologues thereof

and functional fragments thereof which include substitutions or insertions, therefore any homologues thereof or functional fragments thereof is being claimed, and no specific location for where the deletion, substitution or insertion or any combination thereof is recited. Thus, the resulting homologues thereof or functional fragments thereof could result in a homologue or functional fragment not taught and enabled by the specification.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:12, the skilled artisan cannot envision the detailed structure of the homologues thereof or functional fragments thereof, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of

amino acids by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Claims 18 and 19 are drawn to SEQ ID NO:12 and 33. However, it is noted that the sequence of SEQ ID NO 33 has no corresponding start or stop codons in the disclosed nucleic acid sequence. The specification does not provide functional or structural characterization of the full-length open reading frame of the instantly claimed peptide of SEQ ID NO:12. The specification does not provide structural characterization of the complete open reading frame of the bacterial peptide, i.e., including a start codon. In the instant case, the classical start codon is missing from the end of the cloned nucleic acid from which the sequence of the polypeptide was derived. The specification alleges functionality as usable as an operon, however similar bacterial peptides in the art are highly variant and begin with a classic start codon. In view of the lack of evidence in the specification as filed, it is apparent that one skilled in the art would recognize that applicants were not in possession, at the time of filing the instant application, of a genus of the bacterial peptides. Absent characterization of the start

codon, the genus of the bacterial peptides comprised in SEQ ID NO:12 or 33 is highly diverse and variant as are the peptides encoding them, applicant was not in possession.

Therefore the full breadths of the claims fail to meet the written description provision of 35 USC 112, first paragraph.

3. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9 and 18-19 are drawn to a method for screening potential drugs or for the detection of virulence wherein the method utilizes a peptide encoded by an operon. However, the claims merely recite utilizing an operon comprising a gene selected from the group. It appears that "utilizing" the operon is the only active step.

The specification does not appear to teach that simply utilizing the operon will result in a method for screening potential drugs, nor does the specification teach that utilizing the operon will result in a method for detecting virulence. Furthermore, the specification does not state what steps are comprised within the method to achieve screening for potential drugs or detecting virulence. The specification fails to teach examples of screening for potential drugs or detecting virulence by simply utilizing the claimed operon. The specification fails to teach such methods. Therefore, the specification fails to enable a method for screening potential drugs or for the detection of virulence wherein the method utilizes a peptide encoded by an operon.

Applicants have provided no guidance to enable one of skill in the art how to use, without undue experimentation, the method for screening potential drugs or for the detection of virulence wherein the method utilizes a peptide encoded by an operon without appropriate positively recited steps. Moreover, there are no examples of said method utilizing the claimed operon. Thus, simply mentioning the utilization of an operon in the claims does not enabled a method that has no recited steps. Given the lack of guidance contained in the specification and the unpredictability for a method that screens for potential drugs or that detects virulence wherein the method utilizes a peptide encoded by an operon, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Furthermore, the specification fails to provide an enabling disclosure for the utilization of the claimed operon that meets the limitations recited in the claims. Applicants' have provided no guidance to enable one of ordinary skill in the art as to how determine, without undue experimentation, a method for screening potential drugs or for the detection of virulence wherein the method utilizes a peptide encoded by an operon. Thus a skilled artisan would have to de novo determine the steps required to perform said methods. Given the lack of guidance contained in the specification and the unpredictability for the methods, one skilled in the art could not make or use the broadly claimed invention without undue experimentation.

4. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide which has the sequence of SEQ ID NO:12, does not reasonably provide enablement for a peptide which has a sequence 30% homologous to a homologue at the amino acid or nucleotide level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims recite 30% homologous to any amino acid or nucleotide level wherein the modification can be obtained by deletion, substitution or insertion of one or more amino acids or nucleotides, however the specification provides no guidance as to what amino acids or nucleotides may or may not be changed without causing a detrimental effect to the peptide to be produced. The claims broadly teach 30% homology which includes substitution or insertion, and no specific location for where the deletion, substitution or insertion or any combination thereof is recited. If 70% of the nucleotides/amino acids are substituted or inserted the resulting peptide will result in a polypeptide not taught and enabled by the specification. Moreover, the scope of the claim is unduly large and it is clear that the skilled artisan will find hundreds of proteins with as little of 30% homology, most of which will be completely unrelated to the listed proteins. The claim thereof includes virtually every protein, any variation thereof, and any fragment.

Neither the claims nor the specification teach how to obtain a 30% homologous peptide by deletion, substitution or insertion of one or more amino acids. There is no guidance as to what nucleotides may or may not be changed without causing a detrimental effect to the polypeptide being claimed, and no specific location for where

the deletion, substitution or insertion or any combination is recited. Thus, the resulting polypeptide could result in a polypeptide not taught and enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any nucleotide in any location within the polypeptide would not predictably result in a stable molecule. The specification does not provide guidance

on how any nucleotide can be substituted or inserted for the production a stable polypeptide nor does the specification provide guidance on how any location can be used to produce a stable polypeptide. No working examples are shown containing the missing information. There are no examples of peptides with only 30% homology to an unknown amino acid or nucleotide level. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable polypeptide. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid or nucleotide at any location to produce this polypeptide. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

5. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 9 and 18-19 are drawn to a method for screening potential drugs or for the detection of virulence wherein the method utilizes a peptide encoded by an operon. However there is no support within the entire application for a method of screening or for the detection of virulence using any peptide, let alone the peptide consisting of SEQ.ID NO:12 or the polynucleotide of SEQ ID NO:33. No passage within the specification recites using such peptides in a method for screening or method of detection. Applicant failed to point to support in the specification for the recited method

and associated steps. Therefore, applicants must specifically point to page and line number support for the newly added amendments or cancel the claims. Therefore, the claims incorporate new matter and are accordingly rejected.

6. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites the phrases "homologue thereof" and "functional fragments thereof." The specification is silent concerning a definition of what constitutes the metes and bounds of such "homologues thereof" and "functional fragments thereof." Therefore, it is unclear and indefinite as to what is encompassed by the phrases. The terms are relative terms that render the claim indefinite. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of skill in the art would not be reasonably apprised of the scope of the invention. Clarification is required to overcome this rejection.

7. Claim 19 recites to a peptide that comprises amino acid sequence SEQ ID NO:33, however SEQ ID NO:33 is a nucleotide sequence. Therefore the claim is unclear as to what the peptide comprises. Clarification is required to overcome the rejection.

8. Claims 9 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. All steps necessary to perform a method of screening for potential drugs and method for detecting virulence have been omitted. The claims merely recite utilizing the operon without reciting any steps to achieve a method for screening for potential drugs or detecting virulence. Moreover, the specification does not teach any steps for such methods. It is noted, that it is unlikely that the same method steps are required to perform a method of screening for potential drugs and a method for detecting virulence, when the specification is silent with respect to both methods. Thus, neither the claims nor the specification teach method steps necessary steps to accomplish a method for screening for potential drugs or detecting virulence; thus the claims are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines
January 23, 2003

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
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